Historical Note
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Milk or albumin? The history of proteinuria before Richard Bright

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Many physicians, historians—and even some nephrologists—remain under the impression that amongst Richard Bright’s major contributions was the first description of proteinuria, which he detected by heating urine in a spoon held over a candle. Despite Bright’s enormous achievements, nothing could be further from the truth.

Frederick Dekkers (1648–1720) and the work of Paracelsus (1493–1541)

In 1664, a chunky, square book based upon a therapeutic approach to medicine was published in Leiden in The Netherlands, by Frederick Dekkers [1], a pupil of Sylvius. In this, he wrote [the original is in Latin, as was the custom of the time]:

“I have also found that these [water of consumptives] when placed on the fire, soon become milky, really smelled like milk, and had the taste of sweet milk; when a drop or two of acetic acid were added to this, and it was then placed in the cool air, shortly a white rennet, namely the caseous part, sank to the bottom, and the oily or buttery part floated up and there was a sweet whey, quite homogeneous, free now of the different parts; wherefrom we might conclude that this urine is a kind of clear and very thin watery chyle, or nourishing fluid”.

This passage has been interpreted by some, since the original suggestion [2] in 1884 of Wilhelm Olivier von Leube (1842–1922), as the first description of albuminuria. William Dock of the Brigham Hospital in Boston, one of the early writers on the history of Nephrology, remarked in 1922 [3]:

“Dekkers’ imagination was too much taken by the similarity between the appearance of the boiled urine and milk. It is evident that the acetic acid was added to confirm the notion that this fluid was milk”.

Although Dekkers gives an often-reproduced illustration of a woman with severe anasarca, he made no connection whatsoever between this state and the changes in the urine. Today, the passage just quoted calls to mind another quotation, from Paracelsus (1493–1541), cited by Gary Eknoyan a few years ago [4] from On the milk of the kidneys, a lecture given in Basel in 1527. Paracelsus pictures food passing from the stomach, then to the liver, being transformed in each (not such a bad guess!) and then to the kidneys for further change...

“the kidneys digest this in turn, and the first product is white, like milk, because of the Sulphur contained in the fluid;... failure of the second digestion in the kidneys will leave the milky product of the first phase unchanged, and milky urine will be voided. If rennet [gastric chymosin] is added to this Kassmaegen, it curdles and produces a whey (moelken) or if vinegar is added, a separation takes place. The deposit is not pus, but milk. I have seen a beggar who voided milk in his urine for five years and this weakened him to death. When he added wine or vinegar to this urine it coagulated, or when he left it for a few days, cream separated on top” [5].

Dekkers may well have had this passage of Paracelsus in mind when he did his experiment. At least to the present author, this in no way sounds like a search for proteinuria!

Paracelsus’ and Dekkers’ ideas were of course still framed by the Galenic concept of the useful elements in food being separated out by the stomach and intestine, and then further refined into nutritive venous blood in the liver, from which it was carried to the tissues. Part of this blood went to the heart, where it was altered further, in conjunction with air from the lungs. The result was arterial blood endued with vital spirit and carried to the tissues: a final refinement was in the

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brain, where air drawn in through the nose produced animal spirit. From these processes arose first black bile, yellow bile and then finally phlegm. It is worth rehearsing these well-known concepts to emphasize that both savants would have been examining the urine to see in what way this fluid could be related to this process of refinement and its byproducts. Paracelsus was struggling to describe a post-Galenic function of the kidney, by suggesting that it helped disperse unwanted products of refinement.

Domenico Cotugno (1736–1822)

In contrast, Domenico Cotugno of Bari [6], physician to the king of the Two Sicilies, the describer of the cochlea and a host of other anatomical discoveries, had the benefit of the work of Harvey and others in overthrowing many Galenic concepts, and also of the beginnings of the 18th century explosion of ideas and investigation usually called ‘the enlightenment’. In a thoroughly ‘modern’ way, writing a century after Dekkers in 1764, he performed an experiment to confirm a hypothesis derived from observations. The fact that his conclusions were totally erroneous should not detract from appreciation of his methodology.

He wrote a case history of a patient with what is now called a nephrotic syndrome, which is well worth quoting in full, in a tiny slim volume published first in 1765 devoted to the sciatic nerve and the cerebrospinal fluid, whose coagulability he studied [7]. Cotugno wrote [again in Latin like Dekkers], after considering fluids derived from inflammations that are coagulable:

“Thus I will show that all the humours of the body which, when secreted naturally from the blood, are not coagulable, frequently become coagulable from serious disturbances. I shall begin with the urine, which everyone knows is not coagulable, but which was seen to coagulate in these experiments of ours which I am about to describe.

A soldier, twenty-eight years old, was stationed for many years at Baiae [which is] very mild and damp. About the end of August he was seized with an intermittent quotidian fever, which strangely broke out in dropsy in five days. At the beginning of September he was brought to my sanatorium [The ‘Ospedale dei Incurabili’ in Naples] and entrusted to my care. He was suffering at this time with immense watery swellings of his whole body, and overwhelmed by the hitherto daily attacks of fever. The dropsy seemed to increase daily, shortly before the paroxysms. The excreta were dry, there was but little urine and he was wholly cast down in mind. . . . [he was treated with ipecac, squills, Peruvian bark and sassafras] . . . but the urine flowed much less and finally the dropsical swellings seemed to grow . . . In this case it seemed best to use cream of tartar [i.e. potassium bitartrate], whose effect in provoking urine without accelerating the pulse I have shown in other experiments. By this remedy the output of urine was increased so that the sick man passed ten or twelve pints of concentrated urine in a night. However since the sick man himself admitted that his drinking had been very slight, it was certain that the enormous quantities of urine were being drawn especially from the waters collected in the dropsy. Although this was shown by the decrease in the distention of the body, it seemed best to settle the argument by a definite experiment, heating the urine. For I had often conclusively shown that the fluid collected under the skin of such dropsical cadavers contained material capable of coagulation, and I hoped that if the sick man passed such fluid by the way of the urine, coagulation would be seen if the material which flowed out were heated; which, as I anticipated, was proved by experiment. For with two pints of this urine exposed to the fire, when scarcely half evaporated, the remainder made a white mass, like egg albumin”.

The fascinating reference to “urine, which is well known not to be coagulable” suggests that in the early and mid 18th century it may have been common to heat urine and other body fluids as part of their examination; but we have few records of such previous experiments. In 1735, Browne Langrish (? –1759), a country doctor in Hampshire in the South of England, used fractional distillation of the urine in an attempt to relate chemistry to disease [8], as Robert Boyle (1627–1691) had attempted with blood in 1684, and had suggested might be performed. However, these experiments of Langrish appear to have been fruitless—perhaps he never came across urine with albumin in it. Cotugno’s tutor was the Dutch chemist Gerhard van Swieten (1700–1772)—to whom his book is dedicated, but Cotugno quotes Marcello Malpighi (1628–1694) as having demonstrated that the pericardial fluid of a cow was not coagulable by heat; he does not quote anyone else specifically as having heated urine before.

He did not acidify his oedematous soldier’s urine at all [9], but simply “exposed it to the fire”. Cotugno had a perfect theory to account for the coagulable urine, which was that it represented the excretion of the (pathological) oedema fluid, and it was thus a good sign!

Several others, including Charles Darwin and Francis Galton’s grandfather Erasmus Darwin (1731–1802), followed this line of thinking on beneficial proteinuria in his Zoonomia of 1797 [10], as did (Baron) Guillaume Dupuytren (1777–1835) of the Hôtel-Dieu in Paris. Cotugno also donated us the term ‘albuminuria’ when likening the (pathological) urine “ovi albuminis persimil非常”，at the end of the passage translated above, although strangely this word apparently did not emerge in print until 1837 [11]. Until then, urine was referred to as ‘albuminous’ or, more commonly and simply, ‘coagulable’, without implication as to the substance(s)
involved. Protide, protein and proteinuria are all upstart words, little more than 100 years old at best. Cotugno could not have known that relatively small quantities of proteins other than albumin were present in the urine. This was not fully appreciated until a century later, after globulins had been described in blood serum [12].

Animal chemists tackle the problem: William Cruickshank (?–ca. 1811)

The Scot William Cruickshank [13,14] (not to be confused with William Cumberland Cruickshank (1745–1800), sometime assistant to William Hunter, who also studied coagulation in blood and lymph, as many previous writers (including myself) have done, as pointed out by Neild [13]) was the next to advance the study of proteinuria. Although little has come down to us about Cruickshank, clearly he was an expert chemist, who (like Lavoisier) was an ordnance chemist, working at Woolwich arsenal in South East London, and also surgeon to that establishment. Cruickshank worked under Surgeon-general John Rollo, who published a well-known work on diabetes in 1797 [15], to which Cruickshank contributed a signed chapter. He had studied the composition of the urine extensively in health and disease, as Louis Vauquelin (1763–1829) and Antoine Fourcroy (1759–1805) were doing in Paris at the same time, part of a tide of chemical exploration of the animal world using the newly forged tools of chemical analysis; new data, ideas and even elements were appearing almost daily (Rollo and Cruickshank discovered strontium in 1814, naming it after the mines at Strontian in his native Scotland). However, Vauquelin and Fourcroy appear not to have been much interested in protein in the urine (although Fourcroy did note coagulable urine in dropsy, in 1800), sometime assistant to William Hunter, who also studied coagulation in blood and lymph, as many previous writers (including myself) have done, as pointed out by Neild [13]) was the next to advance the study of proteinuria. Although little has come down to us about Cruickshank, clearly he was an expert chemist, working at Woolwich arsenal in South East London, and also surgeon to that establishment. Cruickshank worked under Surgeon-general John Rollo, who published a well-known work on diabetes in 1797 [15], to which Cruickshank contributed a signed chapter. He had studied the composition of the urine extensively in health and disease, as Louis Vauquelin (1763–1829) and Antoine Fourcroy (1759–1805) were doing in Paris at the same time, part of a tide of chemical exploration of the animal world using the newly forged tools of chemical analysis; new data, ideas and even elements were appearing almost daily (Rollo and Cruickshank discovered strontium in 1814, naming it after the mines at Strontian in his native Scotland). However, Vauquelin and Fourcroy appear not to have been much interested in protein in the urine (although Fourcroy did note coagulable urine in dropsy, in 1800), as they were motivated more by a desire to understand the origins of renal stones. Cruickshank employed acid as well as heat alone as a precipitant for albumin in the urine:

“Nitrous acid when added to healthy urine... produces no precipitation. In some diseases however, particularly general dropsy or ascites, this reagent... produces a milkiness [milk again!—author’s note] and in some cases a coagulation similar to... the serum of the blood. Corrosive muriat of mercury [i.e mercuric chloride] in some degree also coagulates drop-sical urine... effects somewhat similar but not so striking are produced by alum. In morbid states of the urine, [the coagulum] is detected... even by heat”.

He goes on:

“in dropsy, the general disease may readily be distinguished from that depending on morbid viscera, by attending to the effects produced on this fluid by nitrous acid and corrosive muriat of mercury. In three cases... the urine coagulated not only on addition of nitrous acid but likewise by heat... the urine appeared to differ but little from the serum of the blood, so remarkable was the coagulation... In the dropsy proceeding from diseased liver and other morbid viscera, the urine does not coagulate either by nitrous acid or by heat”.

By ‘morbid viscera’ Cruickshank meant diseases of liver or heart, which were known by this time to be associated with dropsy. However (contrary to the suggestion of Neild [13]), he appears to me to have had no means of relating this ‘general form’ to the kidney, although of course—like even Galen—he must have been aware where urine came from.

Brande, Wells and Blackall

This important distinction of dropsies was confirmed in 1807 [16] by the physician, chemist and apothecary William Brande (1788–1866), in two patients referred to him by Dr Matthew Baillie (1761–1823), one of the noted surgeons of the day. Brande described the urine of an oedematous man of 67 years.

“long subject to cough... the chief peculiarities of this urine consisted in the abundance of albumen, the deficiency of urea and the presence of the rosac acid of Proust”.

He contrasted this with the urine of man of about 65 “who had laboured for some months under symptoms of a diseased liver... accompanied by ascites”, whose urine contained “a much larger portion of urea [and] afforded no signs of albumin”.

Brande appears to have been the first to note “a deficiency of urea” in the urine of dropscial subjects, an observation later emphasized in 1820 by William Alison (1790–1859) of Edinburgh, and also by John Bostock (see below). From 1800 onwards, therefore, a number of physicians tested the urine by heat in dropscial and other patients, although it did not become a standard part of the examination until after Bright’s book of 1827. In 1811, Pierre-Hubert Nysten (1774–1818) re-iterated in Paris Hippocrates’ observation of persistently frothy urine associated with albuminuria, this time relating it clearly to dropsy.

None of these physicians and chemists of the 1790s and early 1800s, however, commented upon the origin of the albumin in the urine, despite Cruickshank’s comments that it resembled serum in its coagulability. It was the brilliant, sad and fascinating William Charles Wells (1757–1815) of Carolina and St Thomas’ Hospital, London [17], who suggested first that this was serum, derived from the blood [18]:

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“there is another part of the blood [besides the red matter] which I have almost always found present in the urine of those affected with dropsy [after scarlatina], which is the serum”.

This idea probably arose to his mind because in this first set of patients with dropsy that he described [18], the presence of red blood in the urine naturally must have led to the supposition that the albumin likewise had its origin from the serum. In his second paper on non-scarlatinal dropsy, he re-emphasized this origin, and even estimated the U/P_albumin ratio in his cases, by dilution of the serum until its degree of coagulum resembled that of the urine [19]. Despite Wells’ perspicacity, he remained trapped into extending the 18th century idea that the serum was lost into the urine because of serious irritation, particularly of the peritoneum (it is conceivable that some of Wells’ patients actually did have peritonitis, as a result of their nephrotic state). He also described patients “in a salivation excited by mercury for the cure of the venereal disease” whose urine was coagulable, which he attributed to the drug.

Attending the presentation of Wells’ second paper was the Exeter physician John Blackall (1771–1860), who already had a major interest in proteinuria. His book of 1814 [20] ran through five editions up to 1824, was widely read, and was cited by Bright in 1827. Blackall made many observations which are detailed in the paper of Fine and English [21]. Here we will note only that the role of mercury (in the form of calomel usually given for syphilis) in inducing as well note only that the role of mercury (in the form of calomel usually given for syphilis) in inducing as well as possibly alleviating proteinuria was defined further, and the idea of albuminuria being a sign of beneficial discharge of dropsical fluid finally was laid to rest.

“proteinuria is not a temporary relief, but a continued symptom of dropsies throughout their whole course... the curative effect of Nature is not a urine loaded with serum, but almost devoid of it”.

Blackall also recorded the blood to be milky on occasion and buffed in dropsy, signs which he took to confirm the inflammatory nature of the disease, and hence the need for bloodletting. However, unlike Wells, Blackall appears to have been uncertain as to the exact origin of the albumin in the urine. This book was in turn cited in Robert Venables’ (1783/4–1872) work of 1824 [22], which illustrates the interest in the urine in dropsy before Bright. These individuals, some of whom like Wells and Blackall in England, and (a little later) Gabriel Andral (1797–1876) and Jean-Baptiste Gregoire Barbier (1776–1865) in Amiens, noted disordered kidneys in one or two of their albuminuric dropsical patients, but without realizing or denying the significance of these observations.

**Bright and Bostock**

Together with those other clinicians, not mentioned here, who related dropsy to disordered kidneys but did not test the urine, these authors all helped set the scene for Richard Bright when he became interested in the subject in 1816, and then later published his epic Reports of Medical Cases in 1827. His seminal achievement was to relate all three of dropsy, coagulable urine and alterations in the kidneys together, with the kidney placed at the centre of the picture as the primary seat of disease. Bright, in fact, did not do most of the urine tests described in that book: the passages giving details of the composition of the urine (and blood) came from John Bostock (1773–1846) [8,23], a chemist as well as a physician, and Bright’s long-time senior colleague. After their work, the scene changed quickly and forever.

**Notes and references**

1. Dekkers F. Exercitationes practice circa Medendi Methodum. Boutensteyn and Luchtmans, Leiden: 1694: 338–339. This book was popular, and ran to several editions up to 1717
8. Langrish B. The modern theory and practice of physic etc. etc. A. Bettesworth and C. Hitch, London: 1735; 90–91
9. Nor did any of the other pioneers of proteinuria discussed here (Brande, Wells, Blackall). John Bostock (1773–1846) the clinician-chemist working with Bright, and Bright himself used heat, in 1825–1826 but Bostock also studied the effects of mercuric chloride, hydrochloric acid, potassium ferricyanide and tannic acid, which appeared to enhance the ability of heat to reveal small quantities of albumin. He mentioned also that acetic acid would aid separation of the coagulum. He speculated and demonstrated that this urinary albumin appeared identical to that in the blood, and in eggs, in all its chemical reactions that he was capable of testing, and noted diminution of albumin in the blood as it increased in the urine. Nor did Pierre Rayer employ acid then heating during the 1830s—although he used nitric acid as an alternative to heat. In 1851, Sir Robert Christison advocated “you should always employ both heat and nitric acid as tests; the best way is to heat the urine first and then try whether the coagulum resists nitric acid... heat alone may separate earthy salts when these abound, but a coagulum which resists both heat and nitric acid can be nothing other than albumin”. The nitric acid test was standardized in 1852 by Johann Florian Heller (1813–1871) of Vienna, using diluted urine and careful layering of acid and urine to produce a disk of coagulum whose thickness reflected the quantity of proteins (all proteins are precipitated by nitric acid, including Bence Jones
proteinuria and tubular proteinuria). The custom of first adding acetic acid, and then heating, seems to have appeared after 1860, and is recommended in most texts in the second half of the 19th century, e.g. Samuel Wilks, writing in 1891.

10. Darwin E. Zoonomia, or the Laws of Organic Life. Johnson, London, 1794; Vol. I: 467–468. Apart from his illustrious descendants, Darwin was best known during his life as a botanist and scientist as well as a popular physician, and was one of the ‘lunar men’ of the Lunatick Society, who met monthly at the full moon in Birmingham (so they could see to get home) and whose other members included Josiah Wedgewood, Joseph Priestley, James Watt and William Withering. (see Uglow J. The Lunar Men. The Friends who Made the Future. Faber and Faber, London, 2002)

11. Martin Solon (F). De l’albuminurie ou hydropisie causée par maladie des reins etc. Bechet Jeune, Paris, 1837. This work included, as well as extensive material on urine testing and chemistry, five coloured plates depicting diseased kidneys

12. The exception to this statement is, of course, the peculiar urinary protein described by Henry Bence Jones (1814–1873) first in 1847 and then definitively in 1848 (On a new substance occurring in the urine of a patient with mollities ossium. Philos Trans 138: 55–62). He used however the term ‘myelopathic albumosuria’ to describe it


19. Wells WC. On the presence of the red matter and serum of blood in the urine of dropsy, which has not originated from scarlet fever. Trans Soc Improv Med Chir Knowl 1812; 3: 194–240. (read June 4th 1811). Wells states that 1/640 dilution of normal serum will just give a visible precipitate on heating: this is equivalent to 110 mg/l—the first definition of the limits of normal albuminuria and similar to the figures used today. Wells observed U/P ratios of greater than 1/5 in his worst cases, i.e. >1 g/l


